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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/310,638	05/12/99	SOREQ H	2391.00096

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KENNETH I KOHN
KOHN & ASSOCIATES
SUITE 410
30500 NORTHWESTERN HWY
FARMINGTON HILLS MI 48334

EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 12/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/310,638	Soreq et al
Examiner	**Group Art Unit**
Deborah Cr uch	1632

☒ Responsive to communication(s) filed on *Oct 4, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-25* is/are pending in the applicat

Of the above, claim(s) *1-10, 15, 16, 21, and 22* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *11-14, 17-20, and 23-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☒ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Applicant's election with traverse of group II, claims 11-14,17-20 and 23-25 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that as all the claims relate to acetylcholinesterase and methods of using the compound in the treatment of patients that the examination of all claims together would be efficient. This is not found persuasive because the burden on the examiner would be undue to provide thorough examination of disparate subject matter as is claimed. This is compounded by the fact that the searches/considerations are not co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-10,15,16, 21 and 22 stand withdrawn from further consideration by the examiner

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

It is noted that in parent application 08/370,156, applicant did comply with the sequence rules. If applicant wishes, a request can be made to transfer the CRF from the parent to the instant application provided there is no new matter. A sample paragraph is included to guide applicant in the request. However, the "Sequence Listing" of the parent can not be so transferred. Applicant needs to file as an amendment to the specification, a paper copy of the sequence listing with instructions as to its entry. Both the transfer of the CRF and the amendment of the sequence listing must be accompanied with assurances that they are identical to each other and to those of the parent, and that no new matter has been entered. A complete response to this office action provides for both the CRF and the sequence listing. Please see the attached Notice to Comply for further instructions.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-14,17-20 and 23-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,932,780. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are of over lapping scope, obvious scope. The instant claims are to a transgenic animal carrying a recombinant DNA expression vector encoding a heterologous Che enzyme or variants of a heterologous Che enzyme and to the animal as a transgenic assay system. Claims 1-9 of '780 are drawn to a transgenic mouse or a transgenic frog tadpole whose genome comprises a transgene comprising an AChEpromoter operably linked to specific seq. id. nos., where the mouse or frog tadpole exhibts changes in its neuromuscular junction structure, and to the mouse or frog tadpole as an assay system. The claims are of obvious as the animals of the instant claims encompass mouse and frog tadpole of the claims in '780, the instant animal and '780 mouse and frog tadpole comprise an Che enzyme transgene. Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to achieve transgenic animals, and an assay system using them, given the transgenic mouse and frog tadpoles, and an assay system using them, of the claims of '780.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-14,17-20 and 23-25 are rejected under 35 U.S.C. 101 because they are not statutory. It is PTO policy not to issue claims that encompass humans (see 1077 OG 24, April 21, 1987). This rejection may be overcome by inserting "non-human" before "animal".

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-14, 17-20 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims state that the transgene can be naturally occurring variants or derivatives of AChEand BChe, synthetic variants of AChEor BChe. However, the specification does not provide for such variants or derivatives in their breadth to convey to the skilled artisan that at the time of the instant invention that applicant had possession of the variants.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the

invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only alternatively spliced variants of AChe, but not point mutations of AChe, any BChEsequence or any insect BChEsequence, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 11-14,17-20 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic mice and frog tadpoles whose genomes comprise a transgene comprising a AChE promoter operatively linked to a DNA sequence encoding a splice variant of human AChE expressing AChE with acetylcholine esterase activity, wherein said sequence is expressed in cells of said mouse and where said mouse or tadpole exhibits changes in its neuromuscular junction structure, and assay systems of said mouse or tadpole, does not provide enablement for the preparation and use of transgenic animals comprising any and all variants of said cholinesterase genes or assay systems of these animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With regard to the breath of "animals" versus "mice", "mouse" or "frog tadpole" and the breadth of the transgene being limited to as above, at the time of filing, the art as a whole recognized that the production of transgenic animals as a whole was unpredictable. Transgenic animals have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). In addition,

"the position effect" and unidentified control elements also were recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). The elements of the particular construct used to make transgenic animals was held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) Journal of Biotechnology, constructs page 275, column 1, 1st paragraph). At the time of filing, it was regarded the art that one could not predict whether a transgene that is expressed in a mouse (or any other animal) will also be expressed efficiently in another animal. This lack of predictability in expression across species is due at least in part to cis acting elements which interact with different trans-acting factors in these other species (Strojek and Wagner (1988) Genetic Engineering para. bridg. pages 238-239). The integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). Furthermore, it was disclosed that "[t]he use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins et al (1996) J. Clinical Invest. , page S39, Summary). These teachings are more relevant in the instant application where the claims are broadly drawn to non-human mammals which express a recombinant DNA expression vector encoding a variety of Che species and variants. The distance between species of mice and frog is too extreme to take that the results in mice and tadpole are predictive for the genus of non-human animal. This especially noteworthy in view of specific teaching above of species variation in expression of the same DNA sequence.

With regard to the production of transgenic animals producing human AChE or human BChE in its mammary gland and milk, the specification does not provide guidance to the artisan at the time of the invention as to the promoter, vector construct, DNA sequence or additional expression regulatory sequences which correlate with the production of a transgenic non-human mammal expressing either human AChE or human BChE in its milk. The art discussed above is relevant to the bioreactor claims as the issues are the same. In particular it is noted that Houdebine et al is specifically directed to bioreactors. The

art additionally provides reasoning as to why more guidance than that provided for in the specification is needed to produce a bioreactor mammal producing either AChE or BChE in its milk. AChE and BChE are glycosylated enzymes, and thus that the glycosylation pattern determines the tissue type choline esterase (Liao et al (1992) page 1235, col. 2, parag. 1, page 1236, col. 1, lines 22-26). In addition, AChE and BChE are membrane anchored, and for function the enzyme may need to be so anchored (Brodbeck et al (1992) page 35, parag. 1, lines 6-7).. The specification provides no guidance as to the extent of glycosylation needed to obtain functional enzyme or if the membrane anchor would present a problem for secretion of the enzyme into milk. As applicant is the first to disclose such bioreactor methods of producing AChE or BChE, it is incumbent upon the specification to provide guidance to the skilled artisan as to how to make and use the mammal for the production of the enzyme. Guidance is needed as to activity as there is no readily apparent reason to produce the enzyme if it is not biologically active in hydrolyzing a choline ester bond.

Thus for these reasons the specification does not enable the claimed invention, and the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-14, 17-20, and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11,13,20 and 23 state "normal human AChE", "normal human BChE", "synthetic variants of AChE and BChE" and "normal insect ChE's". It is noted that normal can be mutants, which appears to be applicant's naturally occurring or synthetic variants. In addition, a variant is a variant with it is isolated from tissue or synthetically made. The metes and bounds of the claims is not clear. Provided there is

support in the specification, applicant may want to use "wild type" instead of "normal", and use "variants" instead of naturally occurring variants or synthetic variants.

Claims 13 and 18 contain the term "substantial" or "substantially" which is vague as there is no clear meaning of the term in the art, and no clear definition in the specification.

Claim 13 is confusing as SEQ ID NO: 20 is not an amino acid sequence.

Claim 23 is confusing as it depends on itself, and there is no previous claim to a transgenic female.

Claim 25 is confusing as there is no SEQ ID NO: 28 disclosed.

The claims are free of the prior art. At the time of the instant invention the art did not teach or suggest the production of transgenic mice or Xenopus whose genome contained and expressed a DNA sequence encoding any human AChE or human BChE.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Karen Hauda, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Kay Pickney, whose telephone number is (703) 305-3553.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1632

Dr. D. Crouch
December 2, 2000